UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,612	07/16/2007	Teruo Okano	GRT/159-102	3397

23117 7590 10/06/2009

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
10/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,612	OKANO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-16 and 21-26* is/are pending in the application.

4a) Of the above claim(s) *25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-16,21-24 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 2, 4, 17-20 have been canceled. Claims 21-26 have been added. Claims 25 and 26 are labeled "Currently Amended" but should have been labeled as "New". Claims 1, 3, 5-16, 21-26 are pending.

Election/Restrictions

Newly submitted claim 25 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the non-human animal does not have to be prepared using the method of claim 22. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 26 has been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 3, 5-16, 21-24 and 26 are under consideration.

Applicant's arguments filed 6-26-09 have been fully considered but they are not persuasive.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 101

The rejection of claims 1-11, 13-20 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter has been withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112

Claims 1, 3, 5-16 remain and claims 21-24 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making an non-human animal having transplanted cancer cells comprising i) preparing a cell culture support coated with poly N-isopropylacrylamide, ii) cultivating cancer cells on the cell culture support at a temperature in which the cells adhere and grow, iii) decreasing the temperature so that the cancer cells detach from the support, and iv) transplanting the detached cancer cells to a non-human animal, does not reasonably provide enablement for any polymer that changes its hydration force as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a method of making an animal having transplanted cancer cells comprising i) preparing a cell culture support coated with a polymer that changes its hydration force in a temperature range of 0-80° C, ii) cultivating cancer cells on the cell culture support at a temperature in which the polymer has weak hydration force, iii) adjusting the temperature so that the polymer has a stronger hydration force and the cultured cancer cells detach in a sheet from the cell culture support without being treated with a proteolytic enzyme, and iv) transplanting the detached cancer cells to a non-human animal.

The specification states JP 05/192138 taught a method of "skin cells cultivation comprising the steps of preparing a cell culture support which has a surface of its base

coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached. This method depends on temperature adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer."

Example 1 describes a "cell culture base was coated with the temperature-responsive polymer poly(N-isopropylacrylamide) in an amount of 2.0 µg/cm2 and the cancer cells NCI-H460 was cultivated (2 x 104 cells were seeded; 37°C in 5% C02). Three days later, the cancer cells (NCI-H460) on the culture base were confirmed to have become confluent; thereafter, a cultured cell moving jig comprising a polyacrylic plate coated with a fibrin gel was gently placed over the cultured cell sheet so that the cultured cancer cells adhered to it; then, the cell culture base was cooled at 20°C for 60 minutes. After the cooling, the detached cell sheet was collected from the jig together with the fibrin gel and a piece of the gel with the adhering cell sheet (7 mm x 17 mm x 2 mm; 5 x 10^5 cells) was transplanted subcutaneously to the back of each of 10 nude mice.

The specification and the art do not teach any polymers that change hydration force in a temperature range of 0-80 degrees C as required by the claim other than poly(N-isopropylacrylamide). In fact, the specification does not enable those of skill to

determine when a polymer's "hydration force" was in a range that allowed it to attach and grow cells and when it was in a range that caused it to detach. It would have required those of skill undue experimentation to determine other polymers that would culture cells on the polymer at one temperature then detach the cells at a different temperature as claimed. Therefore, the claims should be limited to using poly(N-isopropylacrylamide).

The claims encompass making any species of non-human animal. Claim 12 is limited to making a nude mouse, rat, mouse, guinea pig rabbit. The specification suggests making a nude mouse, rat, mouse, guinea pig rabbit and exemplifies making a nude mouse. However, for the animal to be a model of human cancer, it must comprise human cancer cells. For the animal to support the growth of human cancer cells, it must not reject the cells. The only means described for maintaining human cancer cells in an animal model is if the animal is immunocompromised, and the only immunocompromised animal described by applicants is a nude mouse. If the animal is not immunocompromised, the cancer cells will be attacked by the host's immune system, be destroyed and fail to create a tumor. The specification does not teach how to use an animal that rejects the cancer cells.

Claims 14 and 16 are drawn to a method of selecting agents that treat tumors by administering a test substance to an animal before and/or after transplanting cancer cells. The claims refer to the method of claim 1; however, the claims are unclear (see 112/2nd). For this rejection, it is assumed the claims are directed to a method of using animals made by the method of claim 1. The claims are not enabled because the

specification does not provide adequate guidance how to perform the method by teaching the specific steps of administering agents, the controls or how to compare the results so that agents that treat cancer are identified. Without such guidance, applicants have left those of skill with undue experimentation to determine the steps for using animals made by the method of claim 1 to identify agents that treat cancer. Clarification is required.

Applicants arguments point to pg 7-8, paragraph 16 and argue other polymers are enabled. Applicants' argument is not persuasive. While the polymers may be part of the invention as broad embodiments of original claims, applicants have not provided any evidence that the polymers on pg 7-8 change hydration force from 0-80˚ or are capable of detaching cells in a sheet as claimed. If the polymers on pg 7-8 change hydration force from 0-80˚ and are capable of detaching cells in a sheet as claimed, then the specific conditions required to detach cells in a sheet are wholly unclear. Applicants do not correlate the poly(N-isopropylacrylamide) polymer to the polymers on pg 7-8 such that those of skill could reasonably expect they change hydration force from 0-80˚ and detach cells in a sheet as claimed. Applicants do not teach the conditions required to detach cells in a sheet using any polymer that changes hydration force from 0-80˚ as broadly claimed.

Applicants argue mouse tumor cells can be used to make a cancer cell transplanted mouse; the mouse does not have to be immunocompromised. Applicants' argument is not true but not persuasive. The claims encompass any cancer cell in any species of non-human animal. While a claim may have non-operative embodiments,

the claims as written encompass exponentially more non-operative embodiments than human cancer cells in an immunocompromised mouse or non-human cancer cells in a non-human animal of the same species.

Claims 1, 3, 5-16 remain and claims 21-24 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear what applicants consider the hydration force of a polymer and a polymer that "changes its hydration force in a temperature range of 0-80˚C". The metes and bounds of hydration force and polymers that change their hydration force from 0-80˚C are not defined in the specification or the art at the time of filing. Therefore, those of skill would not know when they were using a polymer that infringed on the claim.

Applicants argue the metes and bounds of the phrase are described on pg 6-9, paragraphs 15-16. Applicants' argument is not persuasive. The paragraphs discuss polymers that can be used in the invention and state the polymer can "changes its hydration force in a temperature range of 0-80˚C" (pg 6, 10 lines from the bottom). The paragraphs do not define or teach how to measure hydration force. Without such guidance, it cannot be determined when a polymer can "change its hydration force in a temperature range of 0-80˚C".

The temperature "region wherein the polymer has weak hydration force" in claim 1 is indefinite. The metes and bounds of when a hydration force is "weak" is not defined

in the specification or art at the time of filing. The specification does not teach how to determine when a polymer is in a temperature range that causes a weak hydration force. Without such guidance, those of skill would not be able to determine when they were infringing on the claim.

Applicants argue the meanings of "weak" hydration forces are "defined in terms of the polymer's hydration and shifts between dehydrated and hydrated states take place at 0-80˚C." Applicants' argument is unclear because the sentence is grammatically incorrect. The specification and the art at the time of filing do not define when a hydration force is "weak;" therefore, those of skill would not be able to determine when they were infringing on the claim.

Likewise, the temperature "at which the polymer has a stronger hydration force" in claim 1 is indefinite. The metes and bounds of when a hydration force is "stronger" is not defined in the specification or art at the time of filing. The specification does not teach how to determine when a polymer is in a temperature range that causes a stronger hydration force. Without such guidance, those of skill would not be able to determine when they were infringing on the claim.

Applicants argue the meanings of "strong" hydration forces are "defined in terms of the polymer's hydration and shifts between dehydrated and hydrated states take place at 0-80˚C." Applicants' argument is unclear because the sentence is grammatically incorrect. The specification and the art at the time of filing do not define when a hydration force is "strong;" therefore, those of skill would not be able to determine when they were infringing on the claim.

The metes and bounds of what applicants consider a specified site in claim 1 is indefinite. It cannot be determined how the adjective "specified" qualifies the structure or function of the site receiving the cancer cell transplant. Applicants do not argue this rejection.

The rejection regarding "sheet" has been withdrawn.

Claim 3 as amended is indefinite because the phrase "wherein the size of a cancer tissue of the non-human animal" is unclear and does not clearly refer back to the sheet of cancer cells transplanted into the animal. The non-human animal of claim 1 does not have "a cancer tissue" until the sheet of cancer cells is transplanted. If the phrase is intended to mean the non-human animal has a tumor and the sheet is added to the tumor to control the size of the tumor, clarification is required. If the phrase is intended to further limit the size of the sheet of tumor cells transplanted or the size of the tumor once the sheet of tumor cells has been transplanted, clarification is required.

The rejection regarding "intimate contact" in claim 5 has been withdrawn in view of the amendment.

Claim 6 is indefinite because the metes and bounds of when a cancer cell is from a "transplantable" cell line. It cannot be determined how "transplantable" qualifies the cell line because all cancer cell lines are transplantable. Claim 7 is indefinite because the metes and bounds of when a cancer cell is from an "untransplantable" cell line. It cannot be determined how "untransplantable" qualifies the cell line because all cancer cell lines are transplantable.

Applicants argue not all cancer cells are transplantable because some would be rejected. Applicants point to Koezuka who used the term. Applicants' arguments are not persuasive. Cancer cells that would be rejected in one animal would not be rejected in an animal with matching self proteins. Cancer cells that would be rejected by an animal are still "transplantable" despite being rejected. The cells described by Koezuka are still able to be transplanted despite being rejected; Koezuka uses the term to describe cells that are rejected in certain animals. Overall, the terms do not further limits the cells in claims 6 or 7.

The metes and bounds of claim 9 are indefinite because all cells are collected from once living tissue. Applicants' argue the cells are derived from living tissue and not post-mortem or another cell culture. Applicants' arguments are not persuasive. Post-mortem tissue is still living; cell metabolism does not shut down in all cells immediately. For example, a tumor removed from a deceased person can be removed and put into culture, i.e. it is "living tissue." Furthermore, all tumor cells isolated from culture were derived from "living tissue" at some point as claimed. Overall, the claim does not further limit the cells.

Claims 14, 16 remain indefinite because they require selecting a substance that reduces the volume and/or weight of a tumor formed from the sheet of cancer cells; however, claim 1 does not require the animal has a tumor formed from the sheet of cancer cells. The claim must set forth the animal develops a tumor, an agent is administered to the animal, parameters of the control and a clear step explaining how to determine agents that treat the tumor. Clarification is required. Applicants argue the

amendment clarifies the claims. Applicants' arguments are not persuasive for reasons set forth in the rejection.

Claim Rejections - 35 USC § 102

Claims 1, 4-7, 9, 12, 13 are newly rejected under 35 U.S.C. 102(b) as being anticipated by Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of applicants' arguments.

This rejection assumes Koezuka taught a poly(N-isopropylacrylamide) polymer as argued by applicants in the response filed 6-26-09, pg 12, and the conditions required to detach cells in a sheet. Detaching cells in a sheet in previous claim 2 is now in claim 1 as amended.

Koezuka taught culturing cancer cells from a primary culture on a thermoresponsive poly(N-isopropylacrylamide) polymer, detaching the cells from the polymer without trypsin and transplanting the cells to nude mice. The conditions described by Koezuka inherently detach cells in a sheet as claimed because the cells are on poly N-isopropylacrylamide polymer and because the conditions are described by applicants as being part of the invention. The claims do not exclude using dextran sulfate or EGTA. Claim 5 is included because it is unclear what applicants consider intimate. Claims 6 and 7 are included because the primary culture described by Koezuka is either a transplantable or untransplantable cell line.

Claim Rejections - 35 USC § 103

Claims 1, 3, 5-13, 15, 16 remain and claims 21-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koezuka (Nippon Nogei Kagaku Kaishi, 1994, Vol. 68, No. 4, pg 783-792, abstract only) in view of Sakai (JP 05/192138).

This rejection assumes Koezuka did not teach the conditions required to detach cells in a sheet as now claimed.

Koezuka taught culturing cancer cells from a primary culture on a thermoresponsive N-isopropylacrylamide polymer, detaching the cells from the polymer without trypsin and transplanting the cells to nude mice. Claim 5 is included because it is unclear what applicants consider intimate. Claims 6 and 7 are included because the primary culture described by Koezuka is either a transplantable or untransplantable cell line. The abstract of Koezuka did not teach using poly(N-isopropylacrylamide) polymer.

However, methods of culturing cells with poly (N-isopropylacrylamide) were known in the art as described by Sakai. The specification states JP 05/192138 taught a method of "skin cells cultivation comprising the steps of preparing a cell culture support which has a surface of its base coated with a polymer having an upper or lower critical temperature for dissolution in water in a range of 0-80°C, cultivating skin cells on the cell culture support at a temperature not higher than the upper critical temperature for dissolution or at a temperature not lower than the lower critical temperature for dissolution, and thereafter adjusting the temperature to above the upper critical temperature for dissolution or below the lower critical temperature for dissolution, whereby the cultured skin cells are detached. This method depends on temperature

adjustment for detaching the cells from the culture base coated with the temperature-responsive polymer." A translator at the patent office confirmed the Japanese patent discusses using poly (N-isopropylacrylamide) as the polymer and states 90% of cells could be peeled off in a sheet from the support as in claim 1 and new claim 22 as amended. Thus, the conditions required to detach cells in a sheet are taught by Sakai.

Thus, it would have been obvious to those of ordinary skill in the art at the time the invention was made to culturing cancer cells on a thermoresponsive polymer and transplant the cells into nude mice as taught by Koezuka wherein the culturing was performed using the conditions for detaching cells in a sheet described by Sakai. Those of ordinary skill in the art would have been motivated to use the conditions for detaching cells in a sheet described by Sakai for ease of manipulation and to prevent leakage of the cells from the site of transplantation. Since the cells are attached to each other in a sheet, they would be less likely to leak from the site of transplantation.

Applicants argue Koezuka taught using a thermo-responsive poly(N-isopropylacrylamide) polymer and dextran sulfate with trypsin. Applicants' argument is not persuasive. Applicants admit the N-isopropylacrylamide polymer described by Koezuka was poly(N-isopropylacrylamide) as claimed. Therefore, Koezuka may be used as a 102 reference upon further prosecution. Secondly, the fourth line from the bottom of the abstract clearly states "without trypsin."

Applicants argue the claimed invention does not require collagen, dextran sulfate or EGTA. Applicants' argument is not persuasive because the claims encompass using (N-isopropylacrylamide) polymer in combination with collagen, dextran sulfate or EGTA.

Applicants argue the Examiner does not provide adequate guidance indicating the combined teachings of Koezuka and Sakai provide adequate guidance to detach the cells in a sheet as claimed. Applicants' argument is not persuasive. Sakai taught how to detach the cells in a sheet. If Koezuka did not teach the conditions required to detach cells in a sheet, the conditions required to detach cells in a sheet are taught by Sakai and would have been obvious to those of ordinary skill in the art at the time of filing; those of ordinary skill in the art at the time of filing would have been motivated to use the conditions described by Sakai that detached cells in a sheet for ease of manipulation and to prevent leakage of the cells from the site of transplantation. Since the cells are attached to each other in a sheet, they would be less likely to leak from the site of transplantation.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517.

The official fax number for this Group is (571) 273-8300.

Michael C. Wilson

/Michael C. Wilson/
Primary Patent Examiner